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Research Article

Efficacy of Cardiac Resynchronization Therapy in Patients with a Narrow QRS Complex

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Aims. In the guidelines for cardiac resynchronization therapy (CRT), there is a gap between the Japanese Circulation Society (JCS) criteria, which specify a QRS duration of ≥120 ms, and other countries, with a QRS ≥ 130 ms. The efficacy of CRT remains controversial in patients with a narrow QRS <130 ms. The aims of this study are to evaluate the response to CRT in patients with a narrow QRS and to identify predictors of mortality. *Methods*. We retrospectively studied 212 patients who received CRT. They were divided into narrow QRS (<130 ms) and wide QRS (≥130 ms) groups. We compared CRT response rates and investigated whether age, gender, baseline New York Heart Association (NYHA) class, ischemic etiology, atrial fibrillation, and ventricular arrhythmias are associated with response and also predictive of mortality. *Results*. The CRT response rate was not significantly different between the wide QRS group and the narrow QRS group (74.6% versus 77.2%, $p = 0.6876$), and the response rate in the narrow QRS group was as good as that reported worldwide. NYHA class IV was shown to be a predictor of mortality (HR 9.38, 95% CI 5.35–16.3, $p < 0.0001$). *Conclusions*. The present study demonstrated that patients with a narrow QRS complex responded well to CRT. Even with QRS <130 ms, CRT should be tried if no other effective treatment is available.

1. Introduction

Despite the fact that cardiac resynchronization therapy (CRT) has been shown to be an effective treatment for heart failure (HF) [1–4], it is clearly underutilized in Japan. According to the Japanese Registry of All Cardiac and Vascular Diseases (JROAD) survey, the number of patients hospitalized for HF in 2017 was 260,000 and is increasing by 10,000 per year [5]. This registry confirmed the data previously recorded in the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) study and data from earlier reports [6, 7]. In contrast, the total number of CRT implantations in combination with either a pacemaker or defibrillator, as reported by the Japan Arrhythmia Device Industry Association (JADIA) in 2017, was about 3300/year [8], and this number has remained fairly static in recent years. While not all HF patients are candidates for CRT, considering the prevalence of interventricular conduction disturbance (IVCD) in HF [9, 10], a somewhat larger increase in the use of CRT would have been expected. Differences in the guidelines between Japan and other countries, especially the European Society of Cardiology (ESC) guidelines [11], primarily account for this underutilization. The Japanese Circulation Society (JCS) guidelines recommend CRT for patients whose QRS is ≥120 ms [12], whereas the ESC guidelines classified patients with a narrow QRS complex of <130 ms as class III. Thus, the current situation has led to some hesitation when considering CRT implantation in patients with a relatively narrow QRS complex, ranging between 120 ms and 130 ms. However, in clinical practice, we deal with numerous cases where patients with a narrow QRS complex of <130 ms respond well to CRT [13–15]. The aim of this study was to evaluate the CRT response in patients with a narrow QRS complex of <130 ms compared with those with wide QRS complex of ≥130 ms.

2. Methods

2.1. Subjects. 269 consecutive patients who underwent CRT implantation at Nihon University Itabashi Hospital between April 2010 and March 2020 were retrospectively studied. CRT was performed according to the Japanese Circulation Society Guidelines in patients who fell into classes I, IIa, and IIb indication [12]. Patients who were upgraded to CRT while receiving right-ventricular pacing because they were pacemaker-dependent were excluded because the intent was different from that of this study. A total of 212 patients were analyzed. Patients were divided into a narrow QRS (<130 ms [range, 120–128], $n = 63$) group and wide QRS (≥130 ms [range, 130–238], $n = 149$) group. We compared CRT response rates between the two groups and performed a multivariable analysis to determine whether QRS duration, LBBB morphology, baseline New York Heart Association (NYHA) functional class IV, ischemic etiology, atrial fibrillation (AF), gender, ventricular arrhythmias, and device type (CRT-P) are predictive of mortality. This study was approved by our institutional ethics committee.

2.2. CRT Programming. AV optimization was performed using automatic optimization, which is incorporated into each device, in order to achieve a narrower QRS compared with the baseline QRS complex. However, if the QRS did not narrow sufficiently with the automatic optimization algorithm, we programmed the AV delay and VV delay manually. We start biventricular pacing with the AV delay 10 ms less than the intrinsic PR interval and prolong the AV delay in 10 ms increments while looking at the QRS width on the ECG; we decided to program the AV delay that yielded the narrowest QRS. We did not optimize VV delay in all cases, but if the QRS did not look narrower following AV delay optimization, we adjusted the VV delay by 10 ms to find the narrowest QRS. CRT reoptimization was performed if the QRS looked wider than the baseline QRS at any clinic visits.

2.3. Definition of CRT Responder. A "CRT response" was defined as having occurred provided the patient met criteria for both functional and echocardiographic responses. A functional response at six-month follow-up was defined as an improvement of at least one grade in "functional status" based on the NYHA class. An echocardiographic response was defined as a reduction in the left ventricular end systolic volume of ≥15% or an improvement in the LVEF (left ventricular ejection fraction) of ≥5% at six months after CRT implantation, based on past clinical trials and reports [1–3, 16, 17]. LVEF was measured by the Simpson method.

2.4. Statistical Analysis. Continuous variables are presented as the mean value ± standard deviation (SD) or standard error (SE). Categorical variables are expressed as total number and percentages. Differences between groups with narrow and wide QRS complex and responder and nonresponder groups were analyzed by *t*-test or chi-square test, as appropriate. Survival was evaluated using the Kaplan-Meier method. The effect of different variables on survival, including age, gender, QRS duration, non-LBBB morphology, NYHA functional class IV, ischemic etiology, presence of AF, ventricular arrhythmias, and CRT-pacemaker usage, was investigated using the Cox proportional hazards model. Variables that showed a statistically significant effect on survival in univariate analyses were entered in a multivariate Cox proportional hazards model, using backward, stepwise selection to obtain the final model. All statistical analyses were performed with JMP 14.0 software (SAS Institute, Cary, NC, USA), and p values < 0.05 were considered significant.

3. Results

3.1. Subjects. The median follow-up period was 35 months [range, 0–192]. The subjects were 170 men and 42 women with a median age of 66 years [range, 14–90]. Mean QRS duration was 145 ± 17 ms with 16% of patients falling into NYHA functional class IV HF. In 74 patients (34%), the etiology could be classified as ischemic. A CRT-pacemaker (CRT-P) was implanted in 62 patients (29%) and a CRT-defibrillator (CRT-D) was implanted in 150 patients.

The baseline characteristics of study patients as well as a comparison between narrow and wide QRS patients are summarized in Table 1. There was no significant difference except QRS duration between the narrow and wide QRS patients.

3.2. CRT Response. As previously described, CRT responder status was determined based on combined assessment of both echocardiographic data and functional status. The echocardiographic data and NYHA functional class obtained before and after CRT implantation as well as the changes in these parameters are shown in Table 2. Reverse remodeling was obtained after CRT implantation in both narrow and wide QRS groups, and none of the parameter changes were significantly different between the two groups. The echocardiographic response rate was 76.4% (74.6% in the narrow QRS group and 77.2% in the wide QRS group); the functional response rate was 85.3% (84.1% in the narrow QRS group and 85.9% in the wide QRS group).

The overall response rate, meeting both criteria, was 76.4%. There was no significant difference in the response rate between the narrow and wide QRS groups (74.6% versus 77.2%, respectively, $p = 0.6876$, Figure 1). As shown in Table 3, in patients with severe HF, there was a significant difference between responder and nonresponder groups (10% versus 30%, $p = 0.0005$, respectively). The overall death rate was significantly lower in the responder group compared with the nonresponder group (31% versus 65%, $p < 0.0001$, respectively). Significant predictors of nonresponse were severe HF (NYHA IV) and ischemic etiology. Multivariate analysis revealed that the strongest predictor of nonresponse to CRT was NYHA IV HF (HR 3.43, 1.55–7.64, $p = 0.0024$). Narrow QRS was not a significant predictor of CRT nonresponse.

3.3. Overall Mortality. During the mean follow-up period of 48 ± 44 months, 85 patients died (40%). Of these deaths, 45 (52%) were due to cardiac causes and 40 (47%) were due to

Table 1: Patient characteristics: overall, narrow, and wide QRS groups.

	Overall ($n = 212$)	Narrow ($n = 63$)	Wide ($n = 149$)	p value
Age (years), mean ± SD	66 ± 13	65 ± 14	67 ± 12	0.2291
Sex, male	171 (81%)	54 (86%)	109 (79%)	0.2152
QRS (ms), mean ± SD	145 ± 17	122 ± 9	159 ± 20	<0.0001
LBBB morphology	140 (66%)	38 (60%)	102 (68%)	0.2560
NYHA class IV	33 (16%)	13 (21%)	20 (13%)	0.1949
Ischemic etiology	83 (39%)	25 (40%)	58 (39%)	0.9179
AF	38 (18%)	11 (17%)	27 (18%)	0.9086
VT/VE history	76 (36%)	20 (33%)	56 (38%)	0.5095
CRT-P (%)	62 (29%)	14 (22%)	48 (32%)	0.1373
LVEF (%), mean ± SD	28.2 ± 9.1	28.2 ± 9.5	28.2 ± 9.0	0.9921
Medication				
Beta-blocker agent	189 (91%)	58 (95%)	131 (90%)	0.1899
ACEI/ARB	138 (67%)	40 (66%)	98 (67%)	0.8296
Diuretics	185 (89%)	56 (92%)	129 (88%)	0.4531
Overall death	84 (39%)	30 (48%)	54 (36%)	0.1235

NYHA: New York Heart Association class; AF: atrial fibrillation; VT/VF: ventricular tachycardia/ventricular fibrillation; CRT-P: cardiac resynchronization pacemaker; LVEF: left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; SD: standard deviation; HF: heart failure.

Table 2: Echocardiographic data and NYHA functional class at baseline and 6 months after CRT implantation.

	Narrow QRS group			Wide QRS group			
	Baseline (mean ± SD)	6 months (mean ± SD)	Delta (mean ± SD)	Baseline (mean ± SD)	6 months (mean ± SD)	Delta (mean ± SD)	p value *
LVEF (%)	28.2 ± 9.5	36.1 ± 9.7	7.9 ± 9.8	28.2 ± 9.0	34.2 ± 11.0	5.9 ± 10.2	0.2768
LVEDV (mL)	223 ± 69	204 ± 65	16 ± 53	214 ± 64	186 ± 75	27 ± 50	0.2584
LVESV (mL)	162 ± 65	134 ± 56	25 ± 50	154 ± 56	127 ± 63	26 ± 43	0.9012
NYHA class	3.1 ± 0.6	2.0 ± 0.8	1.0 ± 0.6	3.0 ± 0.5	1.9 ± 0.8	1.1 ± 0.6	0.6453

LVEF: left ventricular ejection fraction; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; "Delta" indicates the difference before and after implantation; SD: standard deviation. *P value difference in delta between narrow and wide QRS groups.

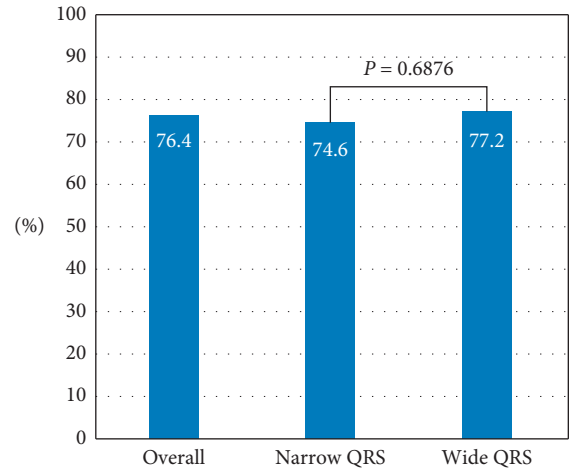

Figure 1: CRT response rate, overall, narrow, and wide QRS groups.

noncardiac causes; in nine patients, the etiology of death could not be determined and was classified as unknown. Overall survival based on QRS duration and NYHA class is shown in Figure 2. After 150 months of follow-up, there was no significant survival difference between the narrow and wide QRS groups ($p = 0.2361$). Of the patients with NYHA class IV HF, just 37% (12/33) were still alive 12 months after CRT implantation. There was a significant difference in

Table 3: Patient characteristics: responders versus nonresponders and predictors of nonresponse to CRT.

	Responder ($n = 155$)	Nonresponder ($n = 57$)	p value	Predictors of nonresponse			
				Univariate OR (95% CI)	P Value	Multivariate OR (95% CI)	p value
Age (years), mean ± SD	66 ± 12	67 ± 13	0.7668	1.00 (0.98–1.03)	0.7646		
Sex, male	121 (78%)	50 (88%)	0.1146	2.01 (0.88–5.20)	0.1016		
QRS (ms), mean ± SD	146 ± 27	144 ± 23	0.5763	1.00 (0.99–1.01)	0.5732		
Narrow QRS (<130 ms)	47 (30%)	16 (28%)	0.7504	0.90 (0.45–1.73)	0.7495	0.80 (0.39–1.60)	0.5396
LBBB morphology	102 (66%)	38 (67%)	0.9066	0.73 (0.36–1.54)	0.4077		
NYHA class IV	16 (10%)	17 (30%)	0.0005	3.69 (1.71–8.03)	0.0010	3.43 (1.55–7.64)	0.0024
Ischemic etiology	52 (34%)	31 (54%)	0.0059	2.36 (1.28–4.41)	0.0063	2.14 (1.13–4.06)	0.0195
AF	25 (16%)	13 (22%)	0.2610	1.54 (0.70–3.22)	0.2703		
VT/VF history	52 (34%)	24 (43%)	0.2254	1.47 (0.78–2.75)	0.2286		
CRT-P (%)	46 (30%)	16 (28%)	0.8196	0.92 (0.46–1.78)	0.8191		
LVEF (%)	28 ± 9.5	28 ± 8.2	0.9772	1.00 (0.96–1.04)	0.9770		
Medication							
Beta-blocker agent	143 (91%)	46 (85%)	0.0634	0.40 (0.90–6.68)	0.0774		
ACE inhibitor/AEB	107 (70%)	31 (57%)	0.0932	0.58 (0.31–1.11)	0.0971		
Diuretics	136 (89%)	49 (91%)	0.7042	1.23 (0.46–3.88)	0.7005		
Overall death	48 (31%)	37 (65%)	<0.0001				

Abbreviations as in Table 1. OR: odds ratio; CI: confidence interval.

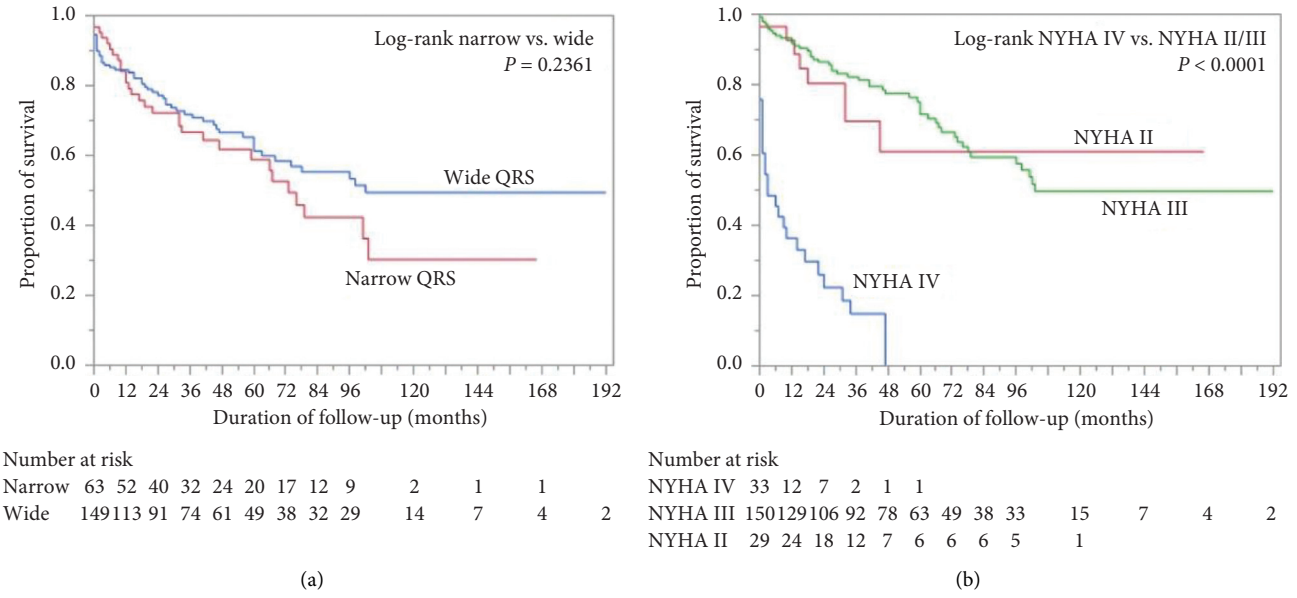

Figure 2: (a) Survival curves for narrow and wide QRS groups. There is no significant difference between the two groups. (b) Overall survival based on severity of heart failure severity. (a) Survival curves: wide QRS versus narrow ORS group. (b) Overall survival based on severity of heart failure at baseline.

prognosis between NYHA class IV and NYHA classes II/III ($p < 0.0001$).

Figure 3 shows the outcome based on QRS. There is no significant difference between narrow and wide QRS groups in HF hospitalization and cardiac death ($p = 0.4125$ and $p = 0.9758$, respectively).

3.4. Predictors of Mortality. Predictors of mortality in all patients are listed in Table 4. Significant univariate predictors of mortality were baseline NYHA class IV (HR 9.25, 95% CI 5.51–15.4, $p < 0.0001$), AF (HR 1.78, 95% CI 1.05–2.89, $p = 0.0328$), absent beta-blocker use (HR 2.18, 95% CI 1.13–3.88, $p = 0.0228$), and absent ACE inhibitor/ARB use (HR 1.82, 95% CI 1.16–2.82, $p = 0.0091$). After adjusting for these variables in a Cox regression model, the strongest predictor of mortality was baseline NYHA functional class IV (HR 9.38, 95% CI 5.35–16.3, $p < 0.0001$).

4. Discussion

4.1. Major Findings. CRT response rate did not differ significantly between patients with narrow and wide QRS. Outcomes consisting of HF hospitalization and cardiac

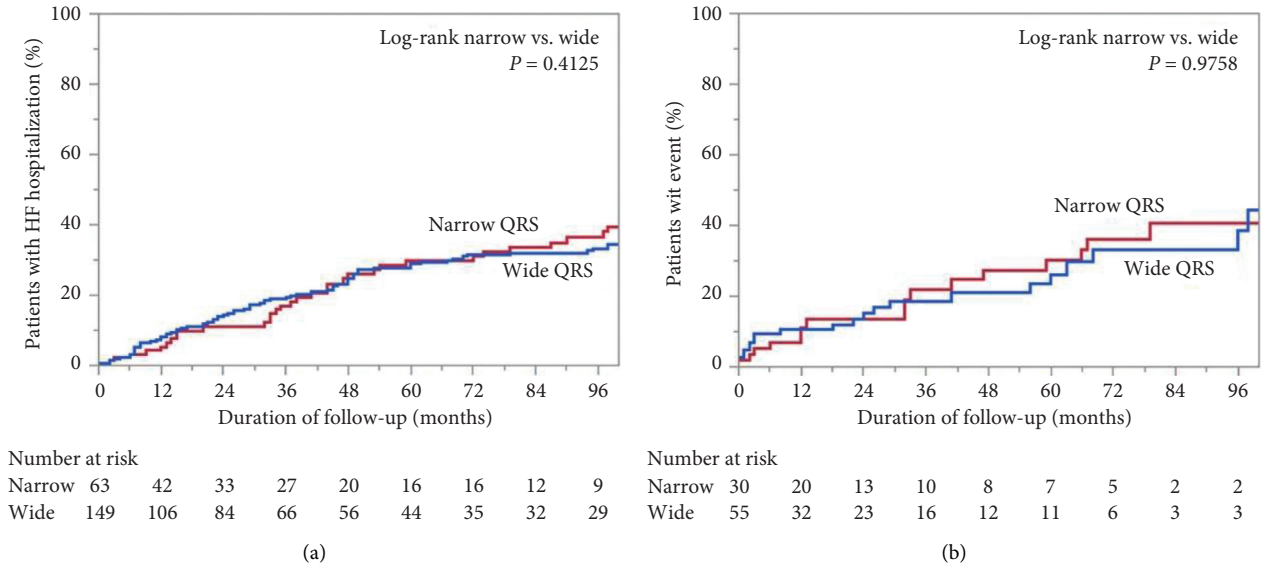

Figure 3: Heart failure hospitalization and cardiac death based on QRS duration. (a) HF hospitalization. (b) Cardiac death.

Table 4: Predictors of all-mortality risk and univariate and multivariate Cox proportional hazards models.

	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
Age	1.00 (0.99–1.02)	0.6417		
Sex, male	1.10 (0.65–2.00)	0.7247		
QRS duration	0.99 (0.99–1.01)	0.1542		
Narrow QRS (<130 ms)	1.27 (0.81–1.97)	0.2933	0.84 (0.51–1.37)	0.4992
LBBB morphology	1.43 (0.90–2.35)	0.1333		
NYHA class IV	9.25 (5.51–15.4)	<0.0001	9.38 (5.35–16.3)	<0.0001
Ischemic etiology	1.45 (0.94–2.22)	0.0952		
AF	1.78 (1.05–2.89)	0.0328	1.66 (0.97–2.72)	0.0655
VT/VF history	1.29 (0.82–2.01)	0.2627		
CRT-P	1.19 (0.75–1.84)	0.4435		
No beta-blocker	2.18 (1.13–3.88)	0.0228	1.97 (0.99–3.62)	0.0544
No ACEI/ARB	1.82 (1.16–2.82)	0.0091	1.37 (0.85–2.16)	0.1907
Diuretic use	1.07 (0.57–2.30)	0.8443		

Abbreviations as in Table 1. HR: hazard ratio; CI: confidence interval.

death were also not significantly different between patients with narrow and wide QRS.

4.2. CRT in Patients with a Narrow QRS Complex. Several previous studies indicate that CRT was not effective in patients with a narrow QRS complex, and CRT is now regarded by many as being highly effective only in patients whose QRS is >150 ms [1–4]. Moreover, it was concluded that CRT is harmful in patients with a narrow QRS of <130 ms [18, 19]. However, some published studies report a positive CRT response in patients with a narrow QRS complex. They describe the efficacy of CRT, as well as the existence of dyssynchrony in patients with a narrow QRS complex [14, 20–22]. Varma et al. reported efficacy in patients with a narrow QRS complex <130 ms from the EchoCRT trial and concluded that CRT may be beneficial in patients with HF with a narrow QRS and smaller ventricles [23]. Indeed, in clinical practice, we often see patients who respond well to CRT despite the fact that their QRS is relatively narrow at <130 ms [15, 24]. In this study, the narrow QRS group had a CRT response rate of 74.6%, which is an acceptable outcome and on a par with that recorded worldwide [1–4, 16].

4.3. AV Optimization in Narrow QRS Patients. It is known that AV optimization is very important for effective CRT. Mullens et al. investigated factors that contribute to CRT nonresponse and found that AV timing is the most frequent reason [25]. We also previously reported favorable outcomes where a nonresponder became a responder after optimization of AV timing [15]. In the cited case, it was challenging to maintain a narrow QRS because the QRS was fairly narrow at baseline. However, we believed that the patient had a conduction disturbance even though the QRS was relatively narrow (less than 130 ms), as shown by the presence of left axis deviation. After trial and error, we finally succeeded. Following this experience, we were convinced that CRT might be used successfully in patients with a narrow QRS.

4.4. Predictors of CRT Nonresponse and Mortality. Most clinical studies show that patients with very severe HF, classified as NYHA class IV, do not respond to CRT and that severity of HF is an independent predictor of CRT nonresponse [1–4, 26]. Our findings agree with those of previous reports that NYHA functional class IV is an independent predictor of nonresponse in both narrow and wide QRS groups. Khatib et al. reported the EAARN (ejection fraction (EF), age, AF, renal dysfunction, and NYHA class IV) score is predictive of mortality in CRT patients [24]. They showed that the strongest predictor of mortality was NYHA class IV HF (HR 2.42, 95% CI 1.62–3.60, $p < 0.001$). Our study also showed that the strongest predictor of mortality was baseline NYHA class IV (HR 9.38, 95% CI 5.35–16.3, $p < 0.0001$). Kaplan-Meier analysis showed that the survival rate 12 months after CRT implantation is just 38% in patients with NYHA class IV HR (Figure 2(b)). These data suggest the importance of implantation of a CRT device at an early stage of HF.

As our data show, HF is a progressive disease and early introduction of therapy is the most effective treatment strategy. In this respect, we regard HF as being very similar to malignant diseases like cancer. It is too late to treat either condition after significant progression. Medication is essential for the treatment of HF, but CRT should be also performed as early as possible if the patient meets the guidelines.

AF was one of the strongest predictors of mortality (HR 1.78, 95% CI 1.05–2.89, $p = 0.0328$); however, after multivariate analysis, this became nonsignificant. The response to CRT might be influenced by the percentage of CRT pacing in patients with AF. We endeavored to maintain a higher pacing rate (over 85%) in CRT patients as part of our CRT management strategy. However, one of the limitations of this study is that we could not ensure an effective pacing rate in all cases, and a pacing rate sufficient to have a clinical effect might not be obtainable in patients with AF.

4.5. Clinical Implications. Our data suggest that patients with a narrow QRS of <130 ms can be expected to respond to CRT in a manner similar to patients with a wide QRS complex. However, the response to CRT differs on a case-by-case basis, but withholding CRT just because the QRS is <130 ms does not seem rational based on the clinical evidence.

4.6. Study Limitations. Our study has several limitations. First, the number of patients with a narrow QRS complex and the number with a wide QRS complex were far from equal, and this may have affected the statistical analysis. Second, the number of patients with NYHA class IV HF and an ischemic etiology for their HF was limited. This may not accord with the distribution seen globally. However, we believe that the distribution of the etiology of HF in Japan corresponds closely to the distribution in our study patients and can provide some useful information in the selection of candidates for CRT. Third, on comparing responder and nonresponder groups, patients with AF were more often nonresponders, and AF remained a predictor of mortality in the wide QRS group; however, the CRT pacing rate is not reported; thus, whether CRT nonresponse was due to an insufficient pacing rate or due to AF itself is unclear.

5. Conclusions

The present study confirms a response to CRT in patients with a narrow QRS complex. Independent predictors of CRT nonresponse and mortality are severe HF in conjunction with NYHA class IV HF. Even patients with a narrow QRS complex of <130 ms had a response rate of >75%, which is on a par with the rate reported worldwide. These results support the idea that the current JCS guidelines are appropriate, at least for Japanese patients, and possibly also for patients with relatively small body size. If heart failure cannot be controlled with medical treatment, CRT should be considered, even in patients with a narrow QRS complex.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

This study was approved by Nihon University Itabashi Hospital, Clinical Research Judging Committee, Reference number: RK-160510-02.

Disclosure

Toshiko Nakai belongs to a department established by contributions from Abbot Medical, Biotronik Japan, Medtronic Japan, Japan Lifeline, and Boston Scientific. Toshiko Nakai received lecture fees from Abbot Medical and Medtronic Japan.

Conflicts of Interest

None of the other authors have conflicts of interest to report.

Authors' Contributions

Toshiko Nakai, Yukitoshi Ikeya, and Yasuo Okumura designed and drafted the manuscript. Rikitake Kogawa, Yoshihiro Aizawa, Ryuta Watanabe, Masaru Arai, and Sayaka Kurokawa acquired data and performed data analysis. Kimie Ohkubo, Daisuke Kitano, and Koichi Nagashima supported the statistical analysis. Toshiko Nakai and Yasuo Okumura substantially contributed to the manuscript and revised it critically for important intellectual content. All authors approved the submitted version.

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